

JC18 Rec'd PCT/PTO 04 MAR 2002

FORM PTO-1390		U S Department of Commerce Patent and Trademark Office	Attorney's Docket No.
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		1604-130	
INTERNATIONAL APPLICATION NO. PCT/ES00/00335		INTERNATIONAL FILING DATE September 1, 2000	PRIORITY DATE CLAIMED September 3, 1999
TITLE OF INVENTION NEW BIOMATERIAL POLYMER SYSTEMS CARRYING TRIFLUSAL OR HTB			
APPLICANT(S) FOR DO/EO/US Alberto Gallardo Ruiz, Gema Rodriguez Crespo, Julio San Roman Del Barrio			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:			
1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under <u>35 U.S.C. 371</u> . 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. 4. <input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input checked="" type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US) 6. <input checked="" type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). a. <input checked="" type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4) 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). ITEMS 11. TO 20. below concern other document(s) or information included: 11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A FIRST preliminary amendment. 14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment 15. <input type="checkbox"/> A substitute specification. 16. <input type="checkbox"/> A change of power of attorney and/or address letter. 17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825 18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4). 19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). 20. <input checked="" type="checkbox"/> Other items or information: - Copy of WO 01/17578 with Search Report			

U.S. APPLICATION NO. (Unknown see 37 CFR 1.50) 10/070244		INTERNATIONAL APPLICATION NO PCT/ES00/00335		ATTORNEY DOCKET NO 1604-130	
<p>21. [X] The following fees are submitted</p> <p>Basic National Fee (37 CFR 1.492)(a)(1)-(5):</p> <p>Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report Not Prepared by EPO or JPO. \$ 1,040.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report has been prepared by the EPO or JPO \$ 890.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$ 740.00</p> <p>International preliminary examination fee (37 CFR 1.482) paid to USPTO but claims did not satisfy provisions of PCT Article 33(1)-(4) \$ 710.00</p> <p>International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$ 100.00</p>				<u>CALCULATIONS</u>	<u>PTO USE ONLY</u>
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$ 1,040.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(c)).				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	30 -20 =	10	X \$18.00	\$ 180.00	
Independent Claims	3 - 3 =	0	X \$84.00	\$ 0	
Multiple dependent claim(s) (if applicable)			+ \$280.00	\$ 280.00	
TOTAL OF ABOVE CALCULATIONS =				\$ 1,500.00	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				\$	
SUBTOTAL =				\$ 1,500.00	
Processing fee of \$130.00 for furnishing the English translation later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				\$	
TOTAL NATIONAL FEE =				\$ 1,500.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$	
TOTAL FEES ENCLOSED =				\$ 1,500.00	
				Amount to be refunded	\$
				charged	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$ 1,500.00 to cover the above fees is enclosed.					
b. <input type="checkbox"/> Please charge my Deposit Account No. 02-2135 in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.					
c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2135. A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO:			<u>Barbara G. Ernst</u> Signature		
Customer No. 6449			<u>Barbara G. Ernst</u> Name		
Barbara G. Ernst Rothwell, Figg, Ernst & Manbeck 555 13th St., N W Washington, D.C. 20004 Phone: 202/783-6040			<u>30,377</u> Registration Number		

1604-130

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
Alberto Gallardo Ruiz et al.) Filing Under 35 USC 371
Serial No.) International Application
Filed:) No. PCT/ES00/00335
For: NEW BIOCOPATIBLE POLYMER)
SYSTEMS CARRYING)
TRIFLUSAL OR HTB)

PRELIMINARY AMENDMENT

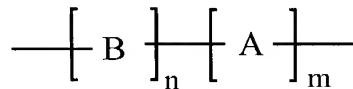
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to examination of the above-referenced patent application, please cancel claims 1-36 and add the following claims:

New Claims

37.- A polymeric compound of relative general formula I



(I)

wherein:

A represents a residue of a polymerisable acrylic or vinylic monomer carrying triflusal or HTB, wherein triflusal or HTB are linked to the remainder of the monomer molecule through an *in vivo* hydrolysable covalent bond;

B represents a residue of a second polymerisable monomer;

m and n represent the molar fractions of the monomers A and B in the polymer so that m + n is always 1 and m is always different from 0;

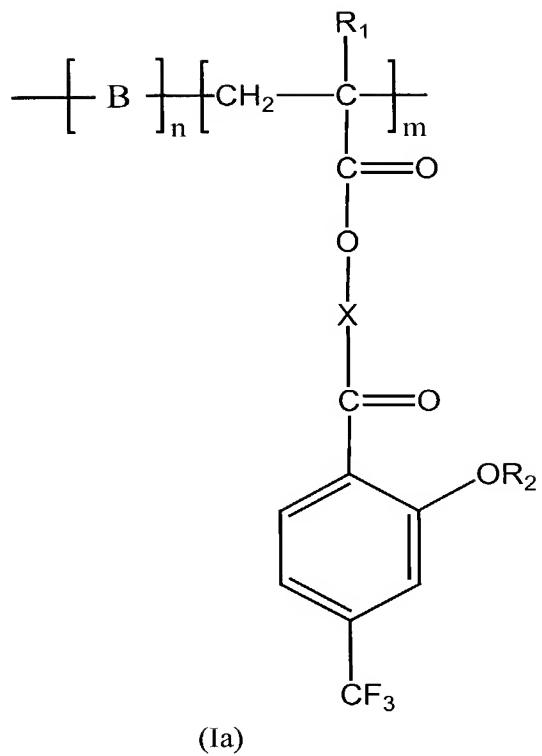
and wherein the A and B units are distributed randomly in the polymer.

38.- A compound according to claim 37 wherein the hydrolysable covalent bond through which triflusal or HTB are linked is a carboxylic ester bond.

39.- A compound according to claim 37 wherein n represents 0.

40.- A compound according to claim 37 wherein n is different from 0.

41.- A compound according to claim 37 of relative formula Ia:



wherein: R_1 represents hydrogen or C_{1-4} alkyl;

R_2 represents $-COCH_3$ or hydrogen;

X represents $-(CH_2CH_2O)_p-$;

p represents an integer from 1 to 100; and

B , m and n have the meaning described in claim 1.

42.- A compound according to claim 41 wherein R_1 represents methyl and p represents 1.

43.- A compound according to claim 42 wherein n represents 0.

44.- A compound according to claim 42 wherein n is different from 0.

45.- A compound according to claim 44 wherein B represents a residue of 2-hydroxyethyl methacrylate, methyl methacrylate, methyl acrylate, N-vinylpyrrolidone, acrylic acid, methacrylic acid, acrylamide, N,N-dimethylacrylamide, vinyl acetate or 2-acrylamido-2-methylpropanesulfonic acid.

46.- A compound according to claim 45 wherein B represents a residue of N,N-dimethylacrylamide.

47.- A compound according to claim 45 wherein B represents a residue of 2-acrylamido-2-methylpropanesulfonic acid.

48.- A compound according to claim 37 having an average molecular weight between 10000 and 100000 Daltons.

49.- A compound according to claim 43 wherein R₂ represents -COCH₃.

50.- A compound according to claim 49 having an average molecular weight of 48000 Daltons, a polydispersity index of 1.8 and ¹H and ¹³C NMR spectra in accordance with the ones shown in figure 3.

51.- A compound according to claim 46 wherein R₂ represents -COCH₃.

52.- A compound according to claim 47 wherein R₂ represents -COCH₃.

53.- A compound according to claim 51 with a molar fraction m of about 0.2 and a molar fraction n of about 0.8, an average molecular weight of 33000 Daltons, a polydispersity index of 2.4 and ¹H and ¹³C NMR spectra in accordance with the ones shown in figure 5.

54.- A compound according to claim 51 with a molar fraction m of about 0.4 and a molar fraction n of about 0.6, an average molecular weight of 34000 Daltons, a polydispersity index of 2.6 and a ¹H NMR spectrum in accordance with that shown in figure 8.

55.- A compound according to claim 51 with a molar fraction m of about 0.6 and a molar fraction n of about 0.4, an average molecular weight of 35000 Daltons, a polydispersity index of 2.5 and a ¹H NMR spectrum in accordance with that shown in figure 7.

56.- A compound according to claim 51 with a molar fraction m of about 0.8 and a molar fraction n of about 0.2, an average molecular weight of 38000 Daltons, a polydispersity index of 2.8 and a ¹H NMR spectrum in accordance with that shown in figure 6.

57.- A compound according to claim 52 with a molar fraction m of about 0.8 and a molar fraction n of about 0.2, an average molecular weight of 43000 Daltons, a polydispersity index of 2.5 and ¹H and ¹³C NMR spectra in accordance with the ones shown in figure 10.

58.- A process for the preparation of a polymeric compound of formula I

according to claim 37 which comprises the radical polymerization of a monomer A and optionally a second monomer B in the molar fractions m and n, respectively, wherein A, B, m and n have the meaning described in claim 37, in the presence of a polymerization initiator, in a suitable solvent.

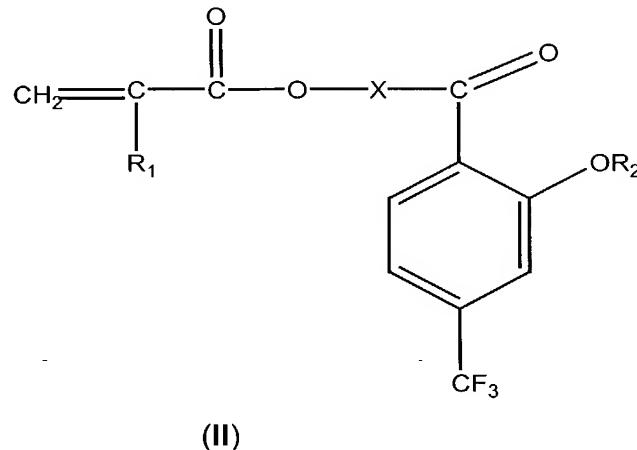
59.- A device or article which comprises a surface of a non-biological material coated with a polymer carrying triflusul or HTB of formula I according to claim 37, wherein said device is suitable for insertion into the body of a mammal and following insertion, is in contact with blood.

60.- A device or article according to claim 59 which is a vascular prosthesis, an artificial cardiac valve or a stent.

61.- Process for preparing a device or article according to claim 59 or 60 which comprises coating said device or article with a polymer carrying triflusul or HTB of formula I according to claim 37.

62.- A pharmaceutical composition which comprises a polymeric compound of formula I according to claim 37 and one or more pharmaceutically acceptable excipients.

63.- A compound of formula II



wherein: R₁ represents hydrogen or C₁₋₄ alkyl;
R₂ represents -COCH₃ or hydrogen;
X represents -(CH₂CH₂O)_p-; and

p represents an integer from 1 to 100.

64.- A compound according to claim 63 wherein R₁ represents methyl and p represents 1.

65.- The compound 2-(methacryloyloxy)ethyl 2-(acetoxy)-4-(trifluoromethyl)benzoate.

REMARKS

The amendments are made to correct improper multiple dependencies and to delete improper claims. No new subject matter has been added.

Respectfully submitted,

By Barbara G. Ernst
Barbara G. Ernst
Attorney for Applicants
Registration No. 30,377
ROTHWELL, FIGG, ERNST & MANBECK, p.c.
Suite 701-E, 555 13th Street, N.W.
Washington, D.C. 20004
Telephone: (202) 783-6040

New biocompatible polymeric systems carrying triflusul or HTB.

The present invention relates to a new series of biocompatible polymeric systems, and more specifically to a new series of biocompatible polymeric systems carrying triflusul or HTB. The invention also relates to a process for their preparation, as well as to their uses, particularly as coatings for prostheses and other devices that are in contact with blood during use.

Background of the invention

The use of synthetic materials in the field of cardiovascular surgery and particularly in the reconstruction of the vascular system has been one of the greatest advances in this field. The materials used must not only possess suitable physicochemical properties such as flexibility, hydrolytic stability and fatigue strength, but it is essential that they exhibit a good blood biocompatibility or hemocompatibility. The contact of the prosthetic devices with the blood flow leads to the deposition of plasmatic proteins on the surface of the material and to the activation of the coagulation cascade, generating a thrombogenic surface.

No material has yet been found that can be regarded in a strict sense as non-thrombogenic, although certain materials have been used with success in the manufacture of big-diameter (> 6 mm) vascular prostheses. Thus, for example, during the last decades commercially available synthetic vascular grafts based mainly on meshes woven or knitted with polyester (Dacron[®]), polyamide (Nylon[®]) or polytetrafluoroethylene (PTFE, Teflon[®]) fibres as well as porous, expanded PTFE (Goretex[®]) systems have been used. Whereas this type of prostheses works relatively well when used to substitute big-diameter vessels, the failure rate at short- or mid-term is quite high when they are used to substitute small- or medium-calibre vessels due to the appearance of thrombosis. It is therefore still necessary to improve the materials used up to now for this kind of applications.

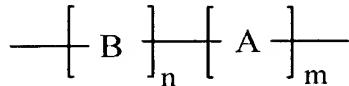
Triflusul, whose chemical name is 2-acetyloxy-4-trifluoromethylbenzoic acid, is a platelet aggregation inhibitor marketed for the treatment of thromboembolic disorders. Its main metabolite, known by the acronym HTB and whose chemical name is 2-hydroxy-4-trifluoromethylbenzoic acid, also exhibits a remarkable platelet aggregation-inhibitory activity. Both compounds are disclosed in the patent US 4,096,252.

The present invention provides a new series of biocompatible polymeric derivatives carrying triflusul or HTB, which, when used as coatings for the surface of prostheses and other devices that are in contact with blood during use, improve

the thrombogenic properties of said devices.

Description of the invention.

The present invention relates to a polymeric compound of relative general formula I



5 (I)

wherein:

A represents a residue of a polymerisable acrylic or vinylic monomer carrying triflusul or HTB, wherein triflusul or HTB are linked to the remainder of the monomer molecule through an *in vivo* hydrolysable covalent bond;

10 B represents a residue of a second polymerisable monomer;

m and n represent the molar fractions of the monomers A and B in the polymer so that m + n is always 1 and m is always different from 0;

and wherein the A and B units are distributed randomly in the polymer.

The present invention also relates to a process for the preparation of a 15 polymeric compound of formula I which comprises the radical polymerization of a monomer A and optionally a second monomer B in the molar fractions m and n, respectively, in the presence of a polymerization initiator, in a suitable solvent.

As mentioned above, the polymeric compounds of the present invention are useful as coatings for the surface of synthetic materials or materials of non- 20 biological origin (to which we will jointly refer throughout the present specification as non-biological materials) which in use are in contact with blood. Due to the fact that the polymers of the present invention carry triflusul or HTB, compounds with a remarkable antiaggregating activity, which are gradually released through the hydrolysis of the covalent bond that links them to the rest of the polymeric system, 25 the application of the polymers of the present invention on the surface of said non-biological materials improves the thrombogenic properties thereof. The polymeric compounds of the present invention can be used in principle to coat any device or article having a surface that is going to be in contact with the blood during use, and specially to coat vascular prostheses, particularly those of small 30 or medium calibre, as well as artificial cardiac valves and stents or vascular springs used in arteriosclerotic processes.

The present invention therefore also relates to the use of a polymeric compound of formula I as coating for non-biological materials, and particularly as coating for vascular prostheses, artificial cardiac valves and stents.

5 The invention further relates to the use of triflusul or HTB for the preparation of biocompatible polymeric compounds for coating non-biological materials, particularly vascular prostheses, artificial cardiac valves and stents.

10 The present invention further relates to a device or article which comprises a surface of a non-biological material that is going to be in contact with blood during use coated with a polymer carrying triflusul or HTB of formula I, and particularly to vascular prostheses, artificial cardiac valves and stents coated with a polymer carrying triflusul or HTB of formula I.

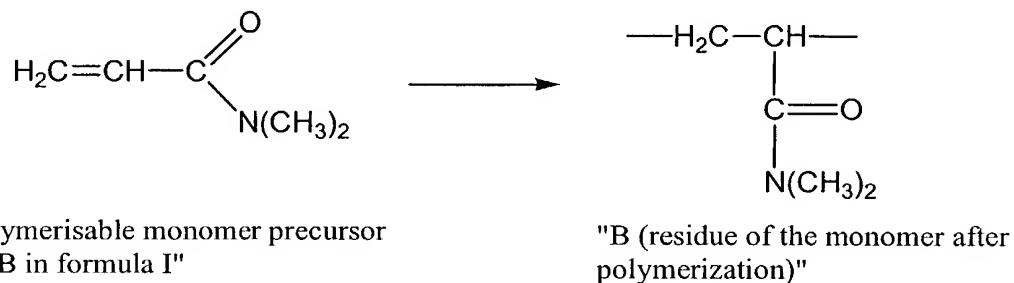
15 The present invention further relates to a process for preparing said devices or articles which comprises coating the desired device or article with a polymer carrying triflusul or HTB of formula I.

20 In the polymeric compounds of the present invention triflusul or HTB are linked to the rest of the polymeric system through hydrolysable covalent bonds. As mentioned above, triflusul or HTB are gradually released through the hydrolysis of said covalent bonds. Due to this, the polymeric compounds of the present invention can also be used as controlled delivery systems for triflusul or 25 HTB and may therefore be useful for the treatment or prevention of all those diseases for which triflusul or HTB are indicated. The present invention therefore also relates to the use of a polymeric compound of formula I as a controlled delivery system for triflusul or HTB, having utility in therapy. Moreover, the present invention also relates to the use of a polymeric compound of formula I for 30 the manufacture of a medicament for the treatment or prevention of the disorders for which triflusul or HTB are indicated and more particularly for the treatment or prevention of thromboembolic disorders. The present invention further relates to a pharmaceutical composition which comprises a polymeric compound of formula I and one or more pharmaceutically acceptable excipients. Said compositions can be prepared following conventional procedures, well known to those skilled in the art.

Throughout the present specification and particularly in formula I, the term residue of a polymerisable monomer, whether acrylic, vinylic or of a different type, shall be understood as the residue resulting from the polymerization of the

corresponding monomer. Thus, for example, when the polymerisable monomer corresponding to B is N,N-dimethylacrylamide, in formula I B represents in fact the residue of said monomer once polymerized, as shown below:

5

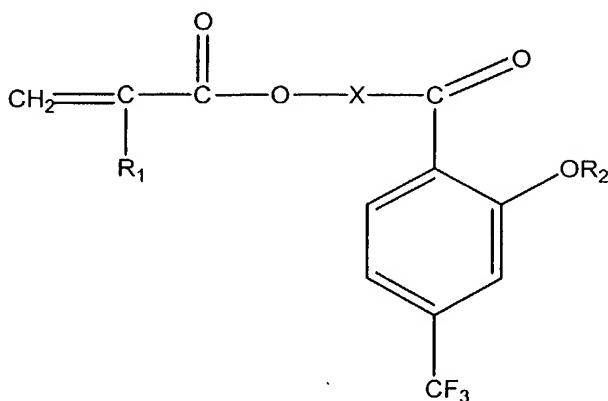


10

Unless otherwise specified, the nomenclature A and B will be used throughout the present specification to refer without distinction to the polymerisable monomer or to the corresponding polymerized residue in the polymer of formula I.

15

In formula I, A represents a residue of any polymerisable acrylic or vinylic monomer carrying trifusal or HTB. The expression "carrying trifusal or HTB" means that the monomer comprises a molecule of trifusal or HTB linked to the rest of the acrylic or vinylic moiety through a covalent bond that is hydrolysable *in vivo*, that is under physiological conditions. A preferred group of monomers carrying trifusal or HTB for the preparation of the polymers of formula I are those corresponding to formula II:



20

(II)

wherein: R₁ represents hydrogen or C₁₋₄ alkyl;

R₂ represents -COCH₃ or hydrogen;

X represents $-(CH_2CH_2O)_p-$; and

p represents an integer from 1 to 100.

Within the compounds of formula II, those compounds wherein R₁ represents methyl and p represents 1 are particularly preferred.

These monomers carrying triflusul or HTB, useful for the preparation of the polymers of formula I, are novel and form a further aspect of the present invention.

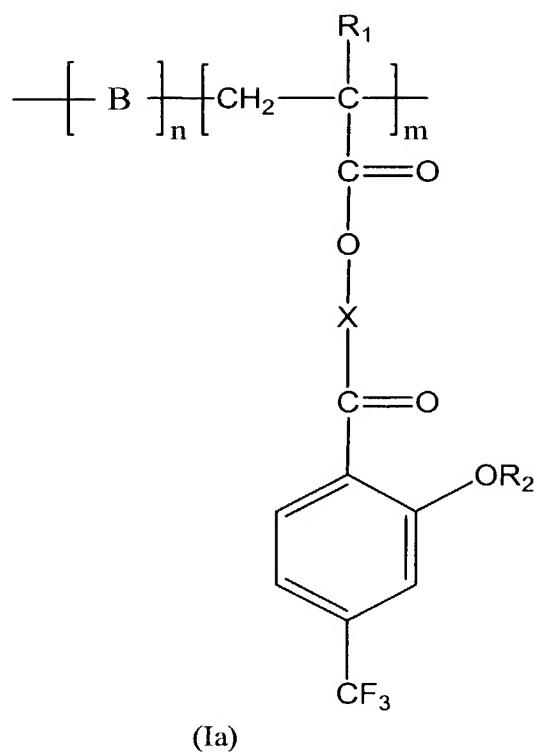
With regard to B, this represents a residue of a second polymerisable monomer, so that when B is present in a polymeric compound of formula I (that is, when n is different from 0) the resulting compound is a copolymer, whereas when B is absent (that is, when n is 0) the resulting compound is a homopolymer. Examples of possible meanings for B include, among others, 2-hydroxyethyl methacrylate, methyl methacrylate, methyl acrylate, N-vinylpyrrolidone, acrylic acid, methacrylic acid, acrylamide, N,N-dimethylacrylamide, vinyl acetate and 2-acrylamido-2-methylpropanesulfonic acid. Furthermore, monomer B can also be another polymerisable monomer carrying triflusal or HTB.

Although the present invention encompasses all the compounds mentioned above, a preferred group of compounds of the present invention are those polymeric compounds of formula I wherein the hydrolysable covalent bond through which triflusal or HTB are linked is a carboxylic ester bond.

Another preferred group of compounds are those compounds of formula I wherein n represents 0.

Another preferred group of compounds are those compounds of formula I wherein n is different from 0.

A more preferred group of compounds of formula I are those polymeric compounds corresponding to relative formula Ia:



wherein: R₁ represents hydrogen or C₁₋₄ alkyl;

R₂ represents -COCH₃ or hydrogen;

X represents $-(CH_2CH_2O)_p-$;

p represents an integer from 1 to 100; and

B, m and n have the previously described meaning.

A still more preferred group of compounds of the present invention are those compounds of formula **Ia** wherein R_1 represents methyl and p represents 1.

10 A particularly preferred group of compounds are those compounds of formula **1a** wherein R₁ represents methyl; p represents 1 and n represents 0.

Another particularly preferred group of compounds are those compounds of formula **Ia** wherein R₁ represents methyl; p represents 1 and n is different from 0. Within this group of compounds, those compounds wherein B represents a residue of 2-hydroxyethyl methacrylate, methyl methacrylate, methyl acrylate, N-vinylpyrrolidone, acrylic acid, methacrylic acid, acrylamide, N,N-dimethylacrylamide, vinyl acetate and 2-acrylamido-2-methylpropanesulfonic acid are preferred, and those compounds wherein B represents a residue of N,N-dimethylacrylamide or 2-acrylamido-2-methylpropanesulfonic acid are still more preferred.

The molecular weight of the polymeric compounds of the present invention can vary within a broad range, being preferred for use as coatings for non-biological materials those polymeric compounds of formula I with an average molecular weight between 10000 and 100000 Daltons.

5 The polymeric compounds of formula I can be prepared by any of the known methods of radical polymerization. For example, they can be prepared by polymerization in a solution of the desired monomer or monomers in a suitable solvent in the presence of a polymerization initiator. Said polymerization must be carried out in the absence of oxygen.

10 As initiator any compound described in the literature for such purpose can be used, for example benzoyl peroxide, lauroyl peroxide, cumene peroxide, butyl perbenzoate, 2,2'-azobisisobutyronitrile (AIBN) or 2,2'-azobisisopentanoic acid, among which benzoyl peroxide and 2,2'-azobisisobutyronitrile are preferred. The amount of initiator to be used will depend upon the molecular weight that it is 15 desired to obtain, and will be easily determined by those skilled in the art.

20 The solvent used to carry out the polymerization can vary depending on the nature of the monomers used; anybody skilled in the art will be able to easily determine the most appropriate solvent for each case. Anyway, as examples of suitable solvents we can mention dioxane, dimethylformamide, isopropanol, dioxane/water mixtures, chloroform, dimethylsulfoxide, acetone, acetone/dioxane mixtures and acetone/water mixtures, among which the use of polar solvents such 25 as dimethylformamide or solvating solvents such as dioxane or dioxane/water mixtures rich in dioxane are preferred.

25 The reaction temperature will depend on the initiator used and will also be a determining factor in the molecular weight of the resulting polymeric system, as will be known by those skilled in the art; in general, a temperature between 50 and 70°C will be appropriate.

30 The time of polymerization required is not too long, due to the nature of the radical polymerization reactions and the fact that they are addition chain reactions; in general we have found that polymerization times between 6 to 24 hours are sufficient to reach high monomer to polymeric system conversions, although in some cases longer polymerization times might be necessary.

The polymers of formula I are finally isolated using conventional methods, for example by precipitation in a suitable solvent such as ethanol, methanol,

isopropanol, hexane, heptane or diethyl ether. In general, it is advisable to use a high precipitant/solution ratio, that is of at least 10 times the volume of precipitant with regard to the volume of solution, to guarantee a good precipitation.

The acrylic or vinylic monomers carrying triflusul or HTB can be prepared in general through the formation of the covalent bond between a suitable acrylic or vinylic derivative and triflusul or HTB, or a reactive derivative thereof, following similar procedures to those described in the literature for the preparation of said type of covalent bonds.

Processes for preparing triflusul or HTB are described in the US patent mentioned above (US 4,096,252).

As stated above, the polymeric compounds of the present invention can be used as coatings for non-biological materials such as prostheses, stents and the like, improving the thrombogenic properties of said materials. Said coatings can be prepared in general by immersion of the surface to be coated in a diluted solution, for example 1-2% w/v, of the desired polymer in a suitable solvent such as dimethylformamide, ethanol, water/ethanol mixtures or dioxane/ethanol mixtures.

Brief description of the figures:

Figure 1 shows the synthesis of the monomer carrying triflusul described in example 1;

Figure 2 shows the synthesis of the polymer described in example 2;

Figure 3 shows the ^1H (3A) and ^{13}C (3B) NMR spectra of the polymer of example 2;

Figure 4 shows the synthesis of a poly[THEMA-co-DMA] copolymer described in example 3;

Figure 5 shows the ^1H (5A) and ^{13}C (5B) NMR spectra of the polymer 3A described in example 3;

Figure 6 shows the ^1H -NMR spectrum of the polymer 3B described in example 3;

Figure 7 shows the ^1H -NMR spectrum of the polymer 3C described in example 3;

Figure 8 shows the ^1H -NMR spectrum of the polymer 3D described in example 3;

Figure 9 shows the synthesis of a poly[THEMA-co-AMPS] copolymer

described in example 4;

Figure 10 shows the ^1H (10A) and ^{13}C (10B) NMR spectra of the polymer described in example 4;

Figure 11 shows the release of HTB from polymer 3A in rat plasma 5 following the method described in example 5.

The following examples are included herein to illustrate the preparation and uses of the compounds of the present invention. In any case they are to be understood as limiting the scope of the invention in any way.

10 In the following examples, polymers were analyzed by ^1H and/or ^{13}C nuclear magnetic resonance (NMR) spectroscopy in the particular conditions mentioned in each case.

15 The molar fractions m and n in the copolymers were determined by ^1H -NMR analysis. Due to the experimental error of the technique, the values of said molar fractions may vary by up to a 5%.

20 The average molecular weights were determined by Gel Permeation Chromatography (GPC) using a Perkin Elmer apparatus equipped with an isocratic pump LC 250 and a refractive index detector series 200. Data were acquired with a PL-DCU (Polymer Laboratories). Samples were eluted using a set of 3 polystyrene – divinylbenzene pL-gel columns of 500, 10^4 and 10^5 Å of nominal pore size (Polymer Laboratories).

Example 1: Preparation of 2-(methacryloyloxy)ethyl 2-acyloxy-4-(trifluoromethyl)benzoate (THEMA)

25 The preparation of this compound is shown in the scheme of Fig. 1.

a) 2-Acyloxy-4-(trifluoromethyl)benzoic acid chloride

30 In a round-bottomed flask 0.1 mols of triflusal were reacted with 70 mL of SOCl_2 , the flask was connected to a refrigerant and the reaction was heated at reflux for 4 h, under magnetic stirring. Next, the unreacted SOCl_2 excess was removed by distillation, first at atmospheric pressure and then at reduced pressure. Then, the desired acid chloride was isolated by distillation at reduced pressure. The yield of the reaction was 64 %.

$^1\text{H-NMR}$ (DMSO- d_6 , 300 MHz, 20°C); δ : 8.1 (d, 1H, arom), 7.7 (d, 1H, arom), 7.6 (s, 1H, arom), 2.3 (s, 3H, $\text{CH}_3\text{COO}-$).

b) 2-(Methacryloyloxy)ethyl 2-acetyloxy-4-(trifluoromethyl)benzoate (THEMA)

In a flask were mixed 0.025 mols of 2-hydroxyethyl methacrylate (HEMA) and 5.21 mL Et₃N (0.025 mols) in 100 mL of diethylether as solvent. To this mixture, 0.025 mols of the acid chloride obtained in step a) dissolved in diethyl ether was added dropwise, under nitrogen flux and at room temperature. Once the acid chloride addition was complete, the reaction was kept under stirring for 24 hours. The precipitated triethylamine hydrochloride was removed by filtration. The filtrate was washed first with water containing some drops of concentrated HCl, and then with water several times. The aqueous phase was discarded and the organic phase was dried over anhydrous MgSO₄. Finally, ether was removed under vacuum until constant weight. The yield of the reaction was 52%.

¹H-NMR (DMSO-d₆, 300 MHz, 20°C); δ: 8.1 (d, 1H, arom), 7.8 (d, 1H, arom), 7.7 (s, 1H, arom), 6.1 and 5.7 (d, m, CH₂=C<), 4.6 and 4.4 (t,t, -CH₂-CH₂-), 2.3 (s, 3H, CH₃COO-), 1.9 (s, 3H, CH₃-C=).

15

Example 2: Preparation of poly[2-(methacryloyloxy)ethyl 2-acetyloxy-4-(trifluoromethyl)benzoate] (poly[THEMA])

This compound was prepared by polymerization of the monomer carrying trifusal obtained in example 1 (THEMA). The chemical structure of this compound and its synthesis are shown in the scheme of Fig. 2.

In Pyrex glass ampoules, 5 g of THEMA (obtained in example 1) was dissolved in 28 mL of a (4:1) purified dioxane/acetone mixture, the concentration of the solution thus being 0.5M. Next, benzoyl peroxide (1.5 x 10⁻² M) was added as the initiator; for the solution described above 100.8 mg were used. Oxygen was then removed from the solution by bubbling nitrogen (30 min) twice.

The sealed ampoules were immersed in a thermostatic bath at 60°C for 24 h. After polymerization, the polymer was precipitated by pouring it into an excess of ethanol; to precipitate 5 g of polymer 500 mL of ethanol was used, to which the polymer solution was added dropwise. This operation was carried out in an ice bath. The solution was kept under stirring for 4 h and was then filtered under vacuum. The precipitate thus obtained was washed several times with ethanol, was filtered again, and was then dried in a high vacuum drying oven until constant weight. The yield of the reaction was 90%.

The average molecular weight of this polymer, determined by Gel Permeation Chromatography (GPC), was 48000 Daltons, with a polydispersity index M_w/M_n of 1.8.

5 The ^1H (400 MHz, CDCl_3 , 45°C) and ^{13}C (100 MHz, DMSO-d_6 , 45°C) NMR spectra of the polymeric compound obtained in this example are shown in Fig. 3 (A and B).

Example 3: Preparation of copolymers from THEMA and N,N-dimethylacrylamide (DMA) having various m/n molar fractions (poly[THEMA-co-DMA])

10 The chemical structure of these copolymers and their synthesis are shown in the scheme of Fig. 4.

The preparation of a representative THEMA-DMA copolymer is carried out as follows:

15 1 g of THEMA (obtained in example 1) and 1 g of DMA was dissolved in 25.75 mL of purified dioxane, the final concentration of the solution being 0.5 M. Next, 46.75 mg of benzoyl peroxide at a concentration of 1.5×10^{-2} M was added and oxygen was removed from the solution by bubbling nitrogen twice for 30 minutes.

20 The sealed ampoule was immersed in a thermostatic bath at 60°C for 24 h. The polymer was then precipitated by pouring the resulting solution dropwise into 1 L of diethyl ether. The solution was kept under stirring for 4 h, diethyl ether was then removed by decantation and the precipitate was dried under vacuum until constant weight. The yield of the reaction was 80%.

25 ^1H -NMR analysis showed that this copolymer (designated from now on polymer 3A) contains a 52 wt % of THEMA with a m/n molar fraction of 0.18/0.82. GPC determination showed that the average molecular weight was 33000 Daltons, with a polydispersity index of 2.4.

30 ^1H (200 MHz, CDCl_3 , 40°C) and ^{13}C (100 MHz, CDCl_3 , 45°C) NMR spectra of polymer 3A are shown in Fig. 5 (A and B).

35 Preparation of other copolymers from THEMA and N,N-dimethylacrylamide (DMA) (poly[THEMA-co-DMA]): Following an analogous procedure to that described to prepare polymer 3A, but changing the proportions of the two monomers (THEMA and DMA) as mentioned below, the following copolymers were obtained:

1) Poly[THEMA-co-DMA] with a molar fraction of 0.20 of DMA in the monomer feed (polymer 3B):

5 0.13 g of DMA and 1.87 g of THEMA was dissolved in 13 mL of purified dioxane (0.5M). Then, 47.2 mg of benzoyl peroxide at a concentration of 1.5×10^{-2} M was added. The experimental conditions for the polymerization and isolation are the same as mentioned above for polymer 3A.

Yield of the polymerization (percentage conversion in weight): 85 %.

Molar fraction m/n = 0.79/0.21

10 Molecular weight M_n = 38000 Dalton

Polydispersity index M_w/M_n = 2.8

15 $^1\text{H-NMR}$ spectrum (200 MHz, CDCl_3 , 40°C): shown in Figure 6.

2) Poly[THEMA-co-DMA] with a molar fraction of 0.40 of DMA in the monomer

15 feed (polymer 3C):

0.31 g of DMA and 1.69 g of THEMA was dissolved in 15.65 mL of purified dioxane (0.5M). Then, 56.81 mg of benzoyl peroxide at a concentration of 1.5×10^{-2} M was added. The experimental conditions for the polymerization and isolation are the same as mentioned above for polymer 3A.

20 Yield of the polymerization (percentage conversion in weight): 91.5 %

Molar fraction m/n = 0.61/0.39

Molecular weight M_n = 35000 Dalton

Polydispersity index M_w/M_n = 2.5

25 $^1\text{H-NMR}$ spectrum (200 MHz, CDCl_3 , 40°C): shown in Figure 7.

3) Poly[THEMA-co-DMA] with a molar fraction of 0.60 of DMA in the monomer feed (polymer 3D):

30 0.58 g of DMA and 1.42 g of THEMA was dissolved in 19.7 mL of purified dioxane (0.5M). Then, 95.98 mg of benzoyl peroxide at a concentration of 1.5×10^{-2} M was added. The experimental conditions for the polymerization and isolation are the same as mentioned above for polymer 3A.

35 Yield of the polymerization (percentage conversion in weight): 89 %

Molar fraction m/n = 0.42/0.58

Molecular weight M_n = 34000 Dalton

Polydispersity index M_w/M_n = 2.6

$^1\text{H-NMR}$ spectrum (200 MHz, CDCl_3 , 40°C): shown in Figure 8.

5 Example 4: Preparation of a copolymer from THEMA and 2-acrylamido-2-methylpropanesulfonic acid (AMPS) (poly[THEMA-co-AMPS])

The chemical structure of this polymer and its preparation are shown in the scheme of Figure 9.

10 To prepare this polymer, 1 g of THEMA (obtained in example 1) and 0.144 g of AMPS was dissolved in 12 mL of (9:1) purified dioxane/water in a Pyrex glass ampoule, the concentration of the solution being 0.25 M. As polymerization initiator, 2,2-azobisisobutyronitrile (AIBN) at a concentration of 1.5×10^{-2} M was used, in this case we used 59.1 mg. Next, N_2 was bubbled through the solution to 15 remove oxygen from the system, twice for 30 minutes.

The sealed flask was immersed in a thermostatic bath at 50°C for 24 h. The solvent was then partly removed using a rotary evaporator and the polymer was then precipitated with 100 mL of diethyl ether. The solution was kept under stirring for 1 h and the solvent was then removed using a rotary evaporator. The 20 residue was dissolved in 10 mL of distilled water and was then freeze-dried. The yield of the process was 100 %.

To purify the polymer, 500 mg of the copolymer obtained was dissolved in 10 mL of chloroform and the copolymer was precipitated by pouring this solution over 100 mL of diethyl ether dropwise, under stirring for 4 h. The polymer was 25 then isolated by filtration under vacuum and was dried until constant weight.

$^1\text{H-NMR}$ analysis showed that the copolymer has a m/n molar fraction of 0.77 in THEMA and 0.23 in AMPS.

The average molecular weight of this polymer, determined by GPC, was 43000 Dalton, with a polydispersity index of 2.5.

30 ^1H (200 MHz, DMSO-d_6 , 40°C) and ^{13}C (300 MHz, DMSO-d_6 , 40 °C) NMR spectra of the copolymer described in this example are shown in figure 10 (A and B).

Example 5: Study of the release of the antiaggregating compound contained in a polymer of formula I in rat plasma

The release of the antiaggregating agent from the polymers of the present invention can be assessed using an *in vitro* assay comprising the incubation at 37° C and under constant stirring of rat plasma to which a solution of the desired polymer has been added and then determine at different times the release of the drug by HPLC. In parallel, and in order to check the linearity and accuracy of the method, the same assay was performed using stock solutions of the drug.

5 a) Plasma preparation

Rat plasma was obtained by cardiac puncture. Animals were placed in a chamber previously saturated with diethyl ether; when animals were anesthetized, 10 they were placed in ventral position and were fastened to a table in order to carry out a cardiac puncture through the intercostal space. Blood was transferred to polypropylene tubes containing 20% of 3.2% sodium citrate as anticoagulant, tubes were closed and homogenized manually. Plasma was obtained by blood centrifugation at 2000 g.

15 b) Solution preparation

For this assay, the polymer 3A obtained in example 3 was used. This polymer carries triflusal. In this case, due to the well-known hydrolysis of triflusal in aqueous media to give its metabolite, HTB, the release of HTB was followed by HPLC.

20 The powdered polymer was dissolved in methanol and solutions having a concentration of 0.96 mg/mL, equivalent to a total HTB concentration of 1.4 mM, were prepared. In parallel, the same assay was performed using HTB stock solutions in order to obtain a suitable calibration curve. The concentrations of HTB used were: 1.25 mM, 1.5 mM, 6.2 mM and 9.3 mM.

25 c) Release assay

The rat plasma prepared as described in step a) was divided into 0.2 mL volumes which were distributed in polypropylene tubes. To each tube, 10 µL of the polymer solution was added. Tubes were immersed in a bath at 37 °C under constant stirring. Aliquots were collected at different times and were analyzed by 30 HPLC, using the following conditions:

- Waters µBoundapak C-18 column of 3.9x300 mm;
- Perkin Elmer LC-250 pump;
- UV/Vis detector Perkin-Elmer LC-95; $\lambda = 305$ nm.
- Waters 770 Data Module integrator

- Mobile phase: aqueous solution of Pic A- methanol, 60:40, microfiltered and degassed.

Before HPLC analysis, samples were prepared by precipitating plasmatic proteins with methanol 1:5, followed by centrifugation at 15000 rpm for 10 min.

5 The supernatant was mixed with an identical volume of mobile phase, microfiltered and injected into the chromatograph.

d) Results

The results obtained in this assay are shown in figure 11, wherein a time-dependent release of HTB from polymer 3A is observed.

10

Example 6: Example of the preparation of a coating with a polymer of formula I

Commercial Goretex® vascular grafts were immersed into a 1:1 dioxane/ethanol solution of the polymer of example 2 (2 wt %) for 30 min. The wet segments of the prostheses were dried at room temperature in a controlled 15 atmosphere of nitrogen until constant weight. The thickness and quantity of the coating was determined by measuring the weight gain of the coated prostheses with respect to the original uncoated prostheses. Homogeneous coatings having a thickness of about 3-5 µm were obtained.

Coated Goretex prostheses were then tested in an extracorporeal circuit 20 and the coating was shown to be stable under blood flux conditions for five days by gravimetry and scanning electron microscopy (SEM).

Similar results were obtained using polymer 3A obtained in example 3.

25 Example 7: Assessment of the thrombogenic properties of a non-biological material coated with a polymer of the invention

The effect of the application of a polymer of the invention as coating of a non-biological material upon the thrombogenic properties of the latter can be evaluated *in vitro* by measuring the platelet aggregation on a material coated with a polymer of the invention in comparison to that observed in the uncoated 30 material; platelet aggregation can be monitored by determining the amount of platelets retained on the material or by scanning electron microscopy (SEM).

a) Method

For this study, platelet-rich plasma (PRP) from sheep arterial blood was used. PRP was isolated by centrifugation of 40 mL blood at 1500 rpm for 10 min.

After this time, the supernatant was discarded and the content of platelets was determined with a hematologic counter Serono-3000. The non-biological material used in this assay were Goretex® vascular grafts of 4 mm inner diameter. A group of prostheses coated with a polymer and a control group (uncoated prostheses) were used.

Prostheses were mounted on seeding chambers and 100 µL of PRP was added. Chambers were incubated at 37 °C in an incubator (5% CO₂) during different periods of time. After the assay time, prostheses were washed three times with MEM (Minimal Essential Medium) to remove non-retained platelets and the number of platelets retained in the prostheses in comparison with the control group was determined indirectly by counting the number of platelets recovered at each of the assay times.

After this, samples were fixed with glutaraldehyde, washed with buffered solution (pH 7.4), dehydrated in a graded acetone series and metallized with gold/palladium for their examination by SEM using a scanning electron microscope Zeiss 950 DSM.

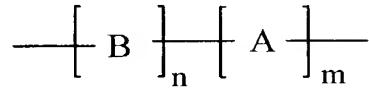
b) Results

Using this assay, it has been observed that the coating of Goretex® prostheses with a thin layer of the polymer obtained in example 2 following the method disclosed in example 6 decreases the retention of platelets in comparison with the uncoated prostheses. In addition, the analysis by SEM shows that platelets are less aggregated in the case of coated prostheses, while the uncoated prostheses (control group) present coagulated domains of aggregated platelets with a strong adhesion to the porous structure of the surface of Goretex®.

These results show the utility of the polymers of the invention to improve the thrombogenic properties of non-biological materials that are in contact with the blood during use.

CLAIMS

1.- A polymeric compound of relative general formula I



5 (I)

wherein:

A represents a residue of a polymerisable acrylic or vinylic monomer carrying triflusul or HTB, wherein triflusul or HTB are linked to the remainder of the monomer molecule through an *in vivo* hydrolysable covalent bond;

10 B represents a residue of a second polymerisable monomer;

m and n represent the molar fractions of the monomers A and B in the polymer so that m + n is always 1 and m is always different from 0;

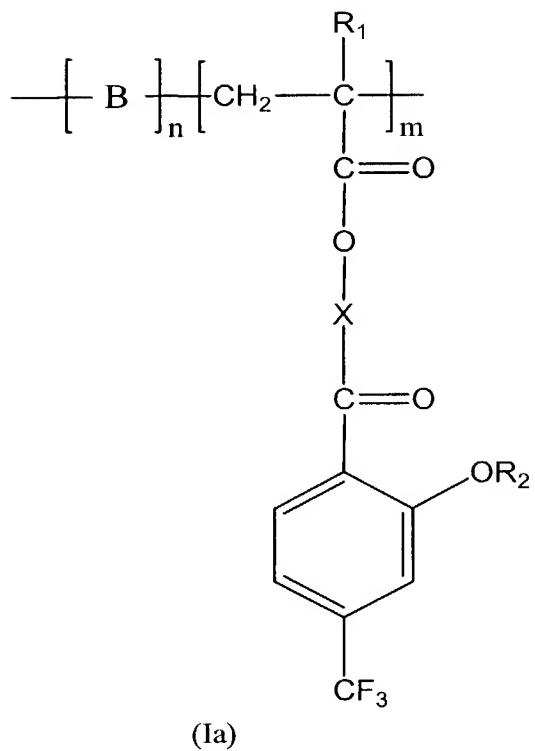
and wherein the A and B units are distributed randomly in the polymer.

2.- A compound according to claim 1 wherein the hydrolysable covalent bond through which triflusul or HTB are linked is a carboxylic ester bond.

15 3.- A compound according to claim 1 wherein n represents 0.

4.- A compound according to claim 1 wherein n is different from 0.

5.- A compound according to claim 1 of relative formula Ia:



wherein: R_1 represents hydrogen or C_{1-4} alkyl;

R₂ represents -COCH₃ or hydrogen;

X represents $-(CH_2CH_2O)_p-$;

p represents an integer from

B, m and n have the meaning described in

ound according to claim 5 wherein R₁ represents

7 - A compound according to claim 6 wherein n represents 0

8. A compound according to claim 6 wherein n is different from

9. A compound according to claim 8 wherein R represents a

3. A compound according to claim 3 wherein B represents a residue of 2-hydroxyethyl methacrylate, methyl methacrylate, methyl acrylate, N-vinylpyrrolidone, acrylic acid, methacrylic acid, acrylamide, N,N-dimethylacrylamide, vinyl acetate or 2-acrylamido-2-methylpropanesulfonic acid.

10.- A compound according to claim 9 wherein B represents a residue of N,N-dimethylacrylamide.

11.- A compound according to claim 9 wherein B represents a residue of 2-acrylamido-2-methylpropanesulfonic acid.

20 12.- A compound according to any of the preceding claims having an average

molecular weight between 10000 and 100000 Daltons.

13.- A compound according to claim 7 wherein R₂ represents -COCH₃.

14.- A compound according to claim 13 having an average molecular weight of 48000 Daltons, a polydispersity index of 1.8 and ¹H and ¹³C NMR spectra in accordance with the ones shown in figure 3.

5 15.- A compound according to claim 10 wherein R₂ represents -COCH₃.

16.- A compound according to claim 11 wherein R₂ represents -COCH₃.

17.- A compound according to claim 15 with a molar fraction m of about 0.2 and a molar fraction n of about 0.8, an average molecular weight of 33000 Daltons, a polydispersity index of 2.4 and ¹H and ¹³C NMR spectra in accordance with the ones shown in figure 5.

10 18.- A compound according to claim 15 with a molar fraction m of about 0.4 and a molar fraction n of about 0.6, an average molecular weight of 34000 Daltons, a polydispersity index of 2.6 and a ¹H NMR spectrum in accordance with that shown 15 in figure 8.

19.- A compound according to claim 15 with a molar fraction m of about 0.6 and a molar fraction n of about 0.4, an average molecular weight of 35000 Daltons, a polydispersity index of 2.5 and a ¹H NMR spectrum in accordance with that shown in figure 7.

20 20.- A compound according to claim 15 with a molar fraction m of about 0.8 and a molar fraction n of about 0.2, an average molecular weight of 38000 Daltons, a polydispersity index of 2.8 and a ¹H NMR spectrum in accordance with that shown in figure 6.

21.- A compound according to claim 16 with a molar fraction m of about 0.8 and a molar fraction n of about 0.2, an average molecular weight of 43000 Daltons, a polydispersity index of 2.5 and ¹H and ¹³C NMR spectra in accordance with the ones shown in figure 10.

25 22.- A process for the preparation of a polymeric compound of formula I according to claim 1 which comprises the radical polymerization of a monomer A and 30 optionally a second monomer B in the molar fractions m and n, respectively, wherein A, B, m and n have the meaning described in claim 1, in the presence of a polymerization initiator, in a suitable solvent.

23.- Use of a polymeric compound of formula I according to any of claims 1 to 21 as coating for non-biological materials.

24.- Use according to claim 23 wherein the non-biological material is a vascular prosthesis, an artificial cardiac valve or a stent.

25.- Use of triflusul or HTB for the preparation of biocompatible polymeric compounds for coating non-biological materials.

5 26.- Use according to claim 25 wherein the non-biological material is a vascular prosthesis, an artificial cardiac valve or a stent.

27.- A device or article which comprises a surface of a non-biological material that is going to be in contact with blood during use coated with a polymer carrying triflusul or HTB of formula I according to any of claims 1 to 21.

10 28.- A device or article according to claim 27 which is a vascular prosthesis, an artificial cardiac valve or a stent.

29.- Process for preparing a device or article according to claim 27 or 28 which comprises coating said device or article with a polymer carrying triflusul or HTB of formula I according to any of claims 1 to 21.

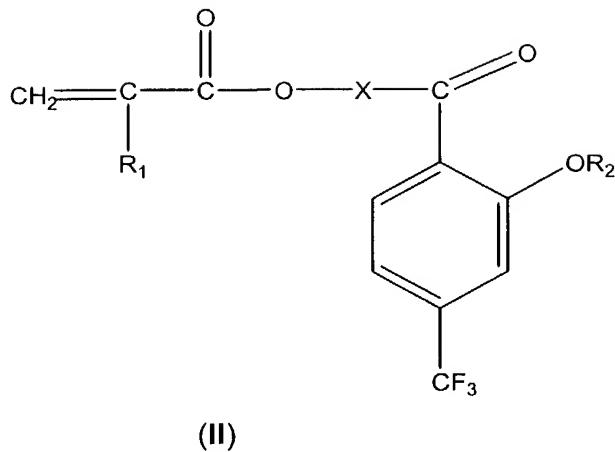
15 30.- Use of a polymeric compound of formula I according to any of claims 1 to 21 as a controlled delivery system for triflusul or HTB.

31.- Use of a polymeric compound of formula I according to any of claims 1 to 21 for the manufacture of a medicament for the treatment or prevention of the disorders for which triflusul or HTB are indicated.

20 32.- Use of a polymeric compound of formula I according to any of claims 1 to 21 for the manufacture of a medicament for the treatment or prevention of thromboembolic disorders.

33.- A pharmaceutical composition which comprises a polymeric compound of formula I according to any of claims 1 to 21 and one or more pharmaceutically acceptable excipients.

25 34.- A compound of formula II



wherein: R_1 represents hydrogen or C_{1-4} alkyl;

5 R_2 represents $-COCH_3$ or hydrogen;

X represents $-(CH_2CH_2O)_p-$; and

p represents an integer from 1 to 100.

35.- A compound according to claim 34 wherein R_1 represents methyl and p represents 1.

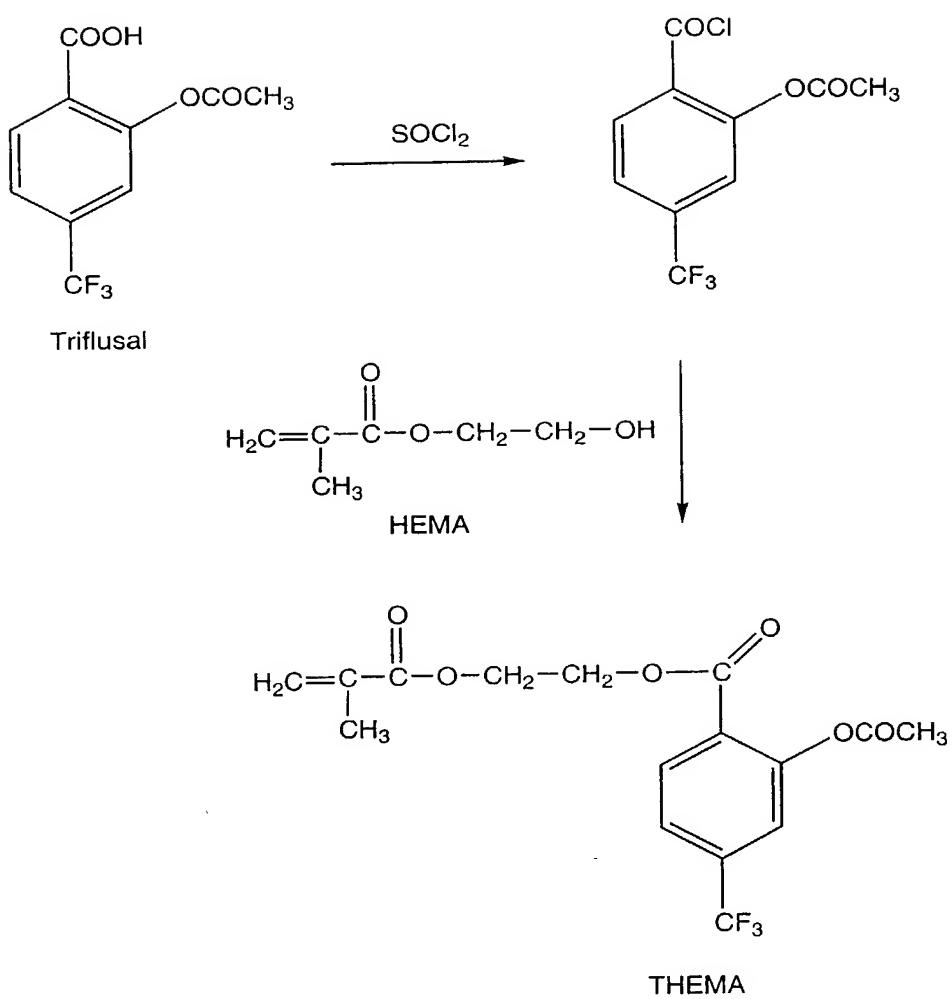
10 36.- The compound 2-(methacryloyloxy)ethyl 2-(acetoxy)-4-(trifluoromethyl)benzoate.

Abstract

New biocompatible polymeric systems carrying triflusal or HTB are described which result from the polymerization of a monomer A of the acrylic or vinylic type 5 and carrying triflusal or HTB, wherein triflusal or HTB are linked to the remainder of the molecule of said monomer through an *in vivo* hydrolysable covalent bond, and optionally a second polymerisable monomer B. These new polymeric systems are useful as coating for synthetic biomaterials.

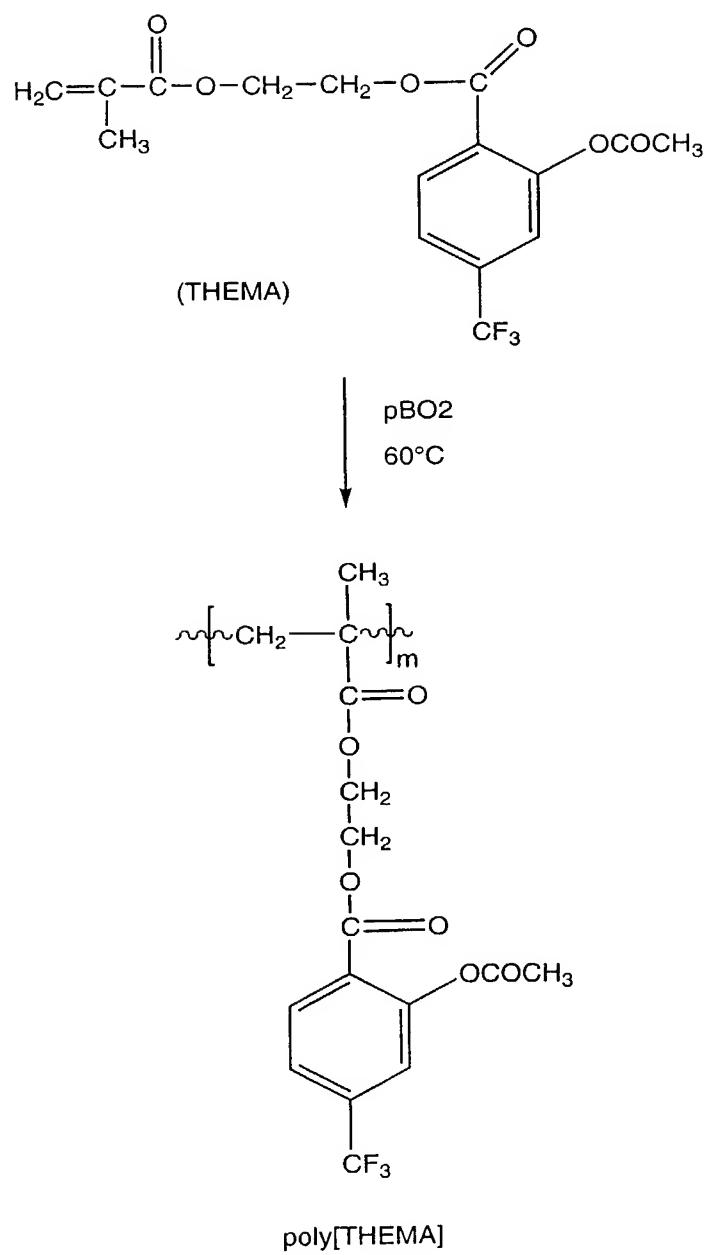
1/14

Fig. 1



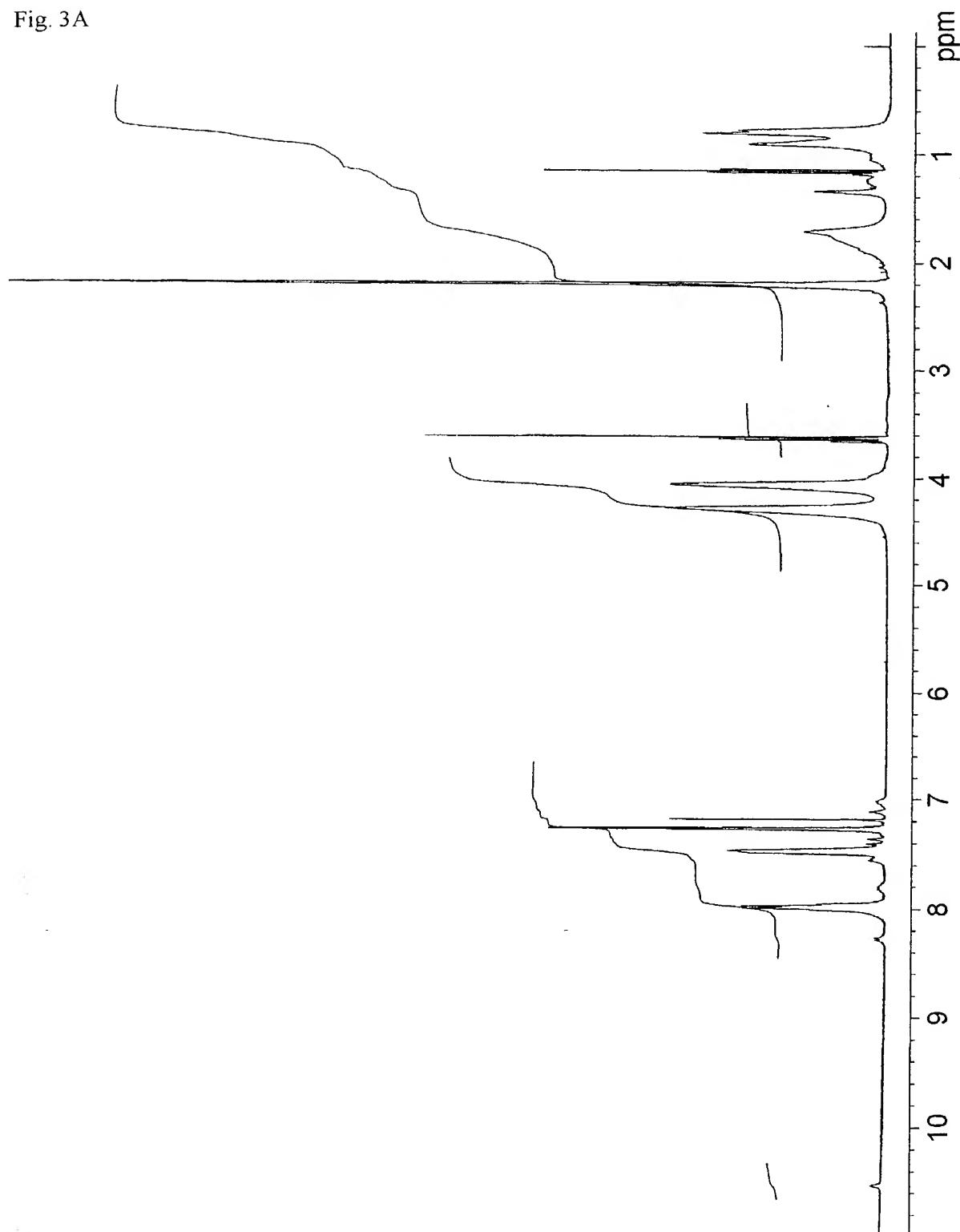
2/14

Fig. 2



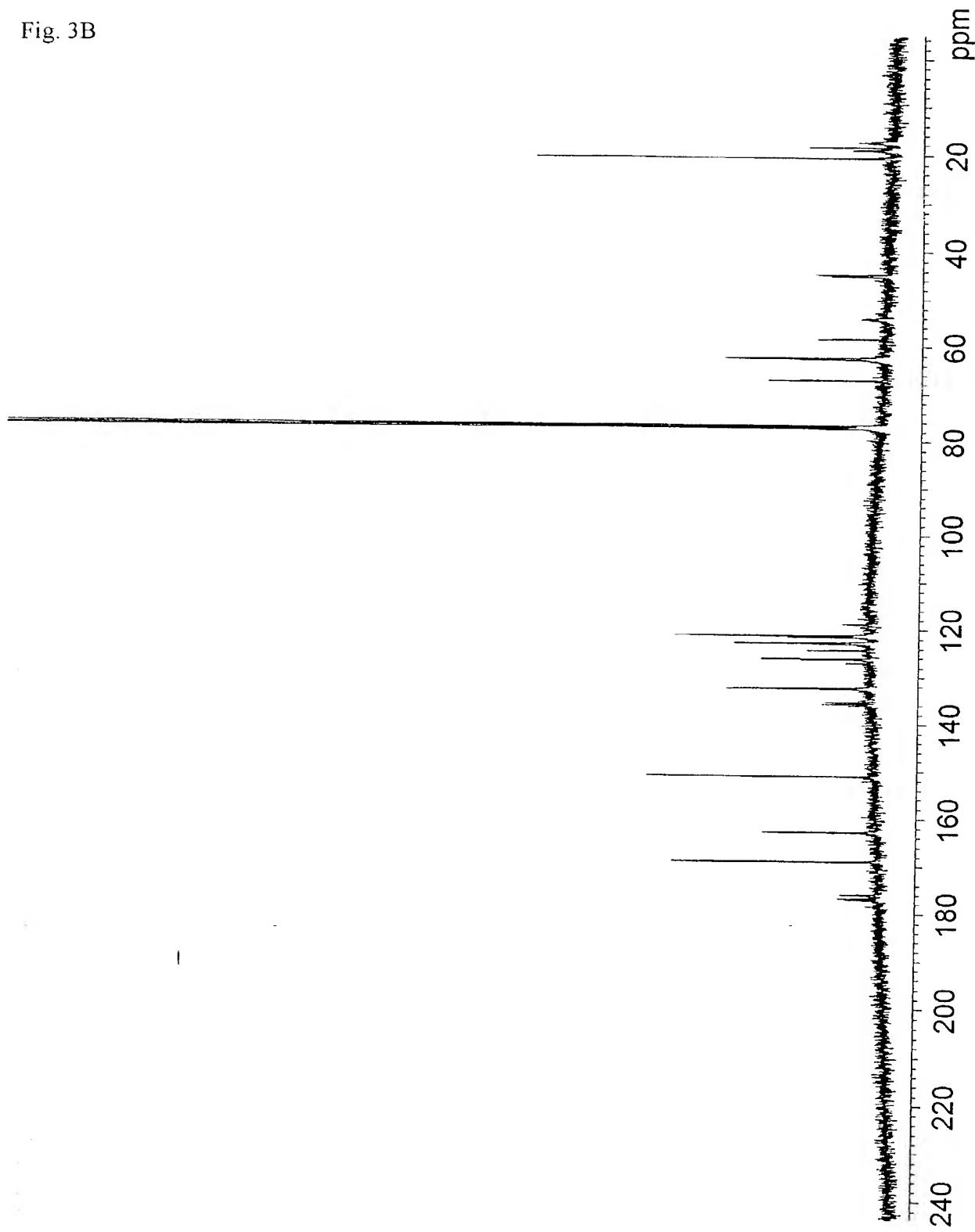
3/14

Fig. 3A



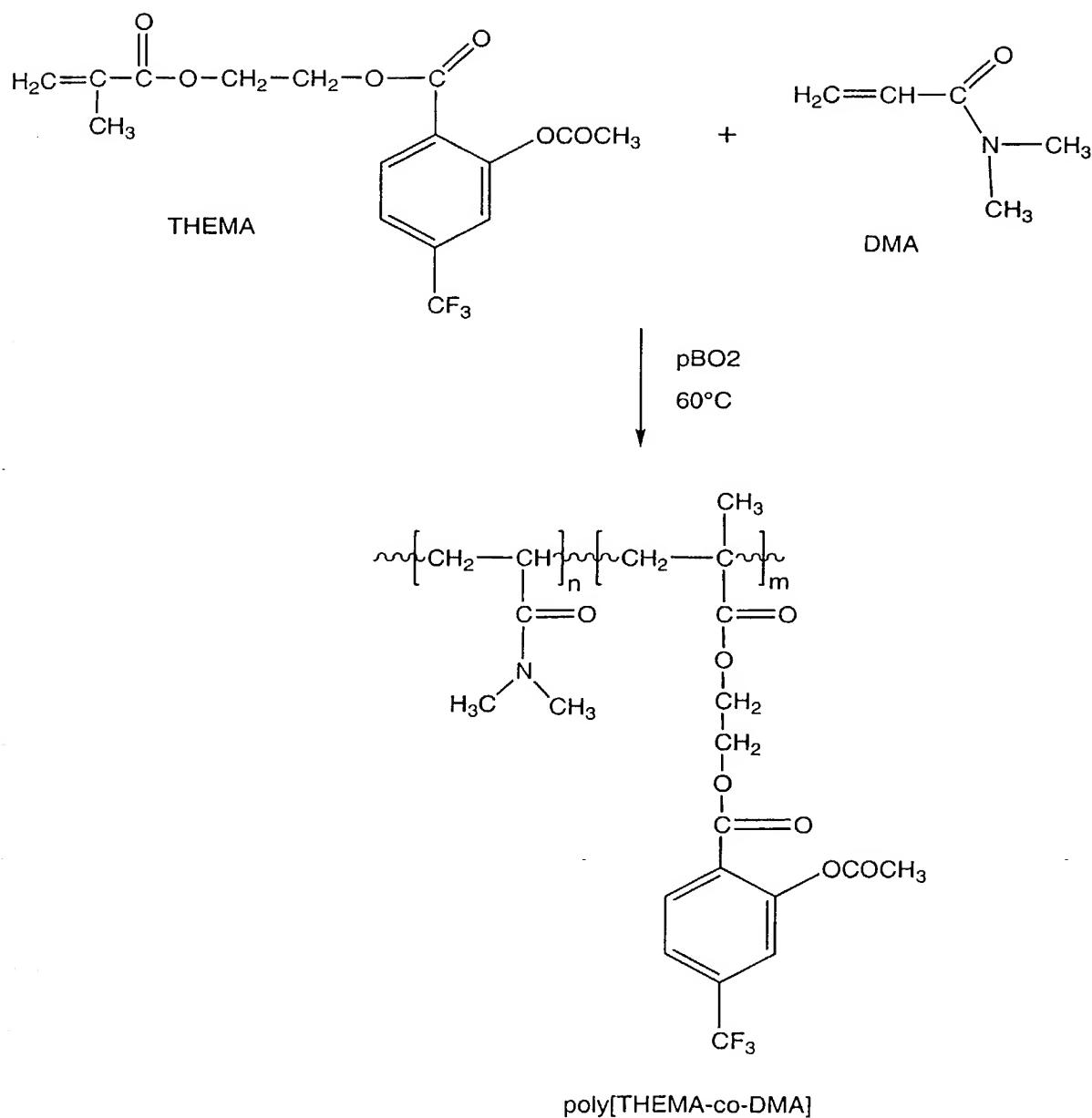
4/14

Fig. 3B



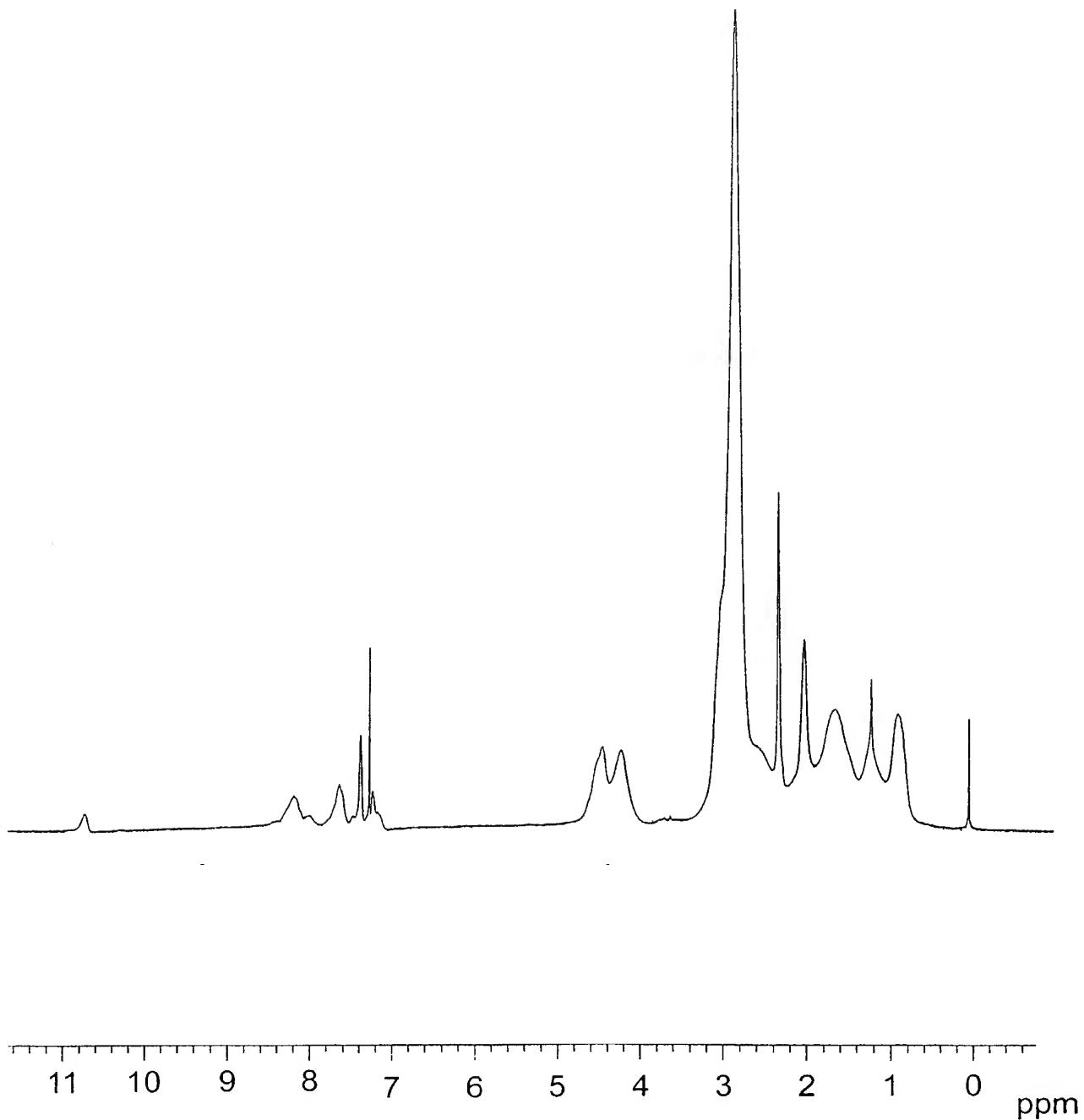
5/14

Fig. 4



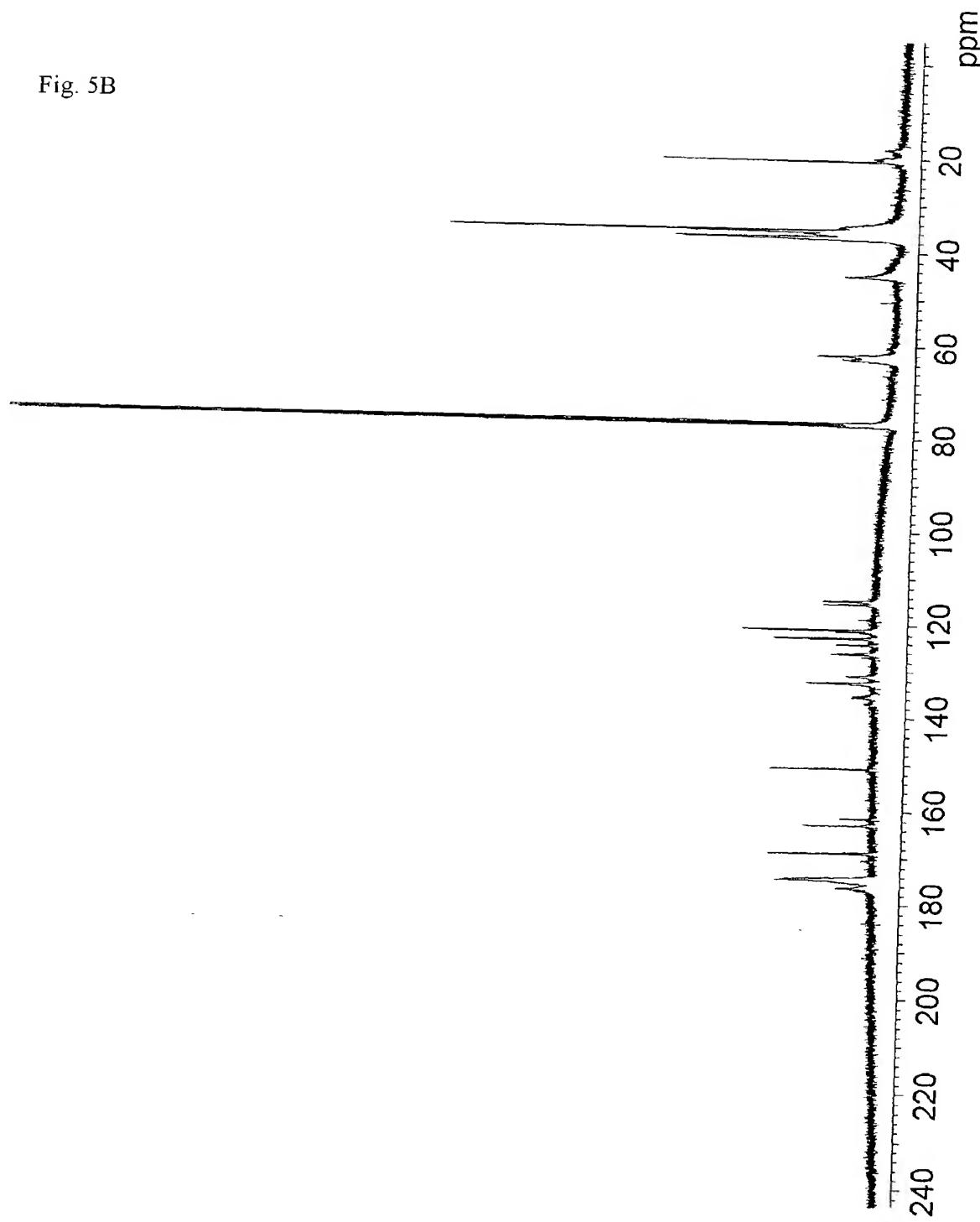
6/14

Fig. 5A



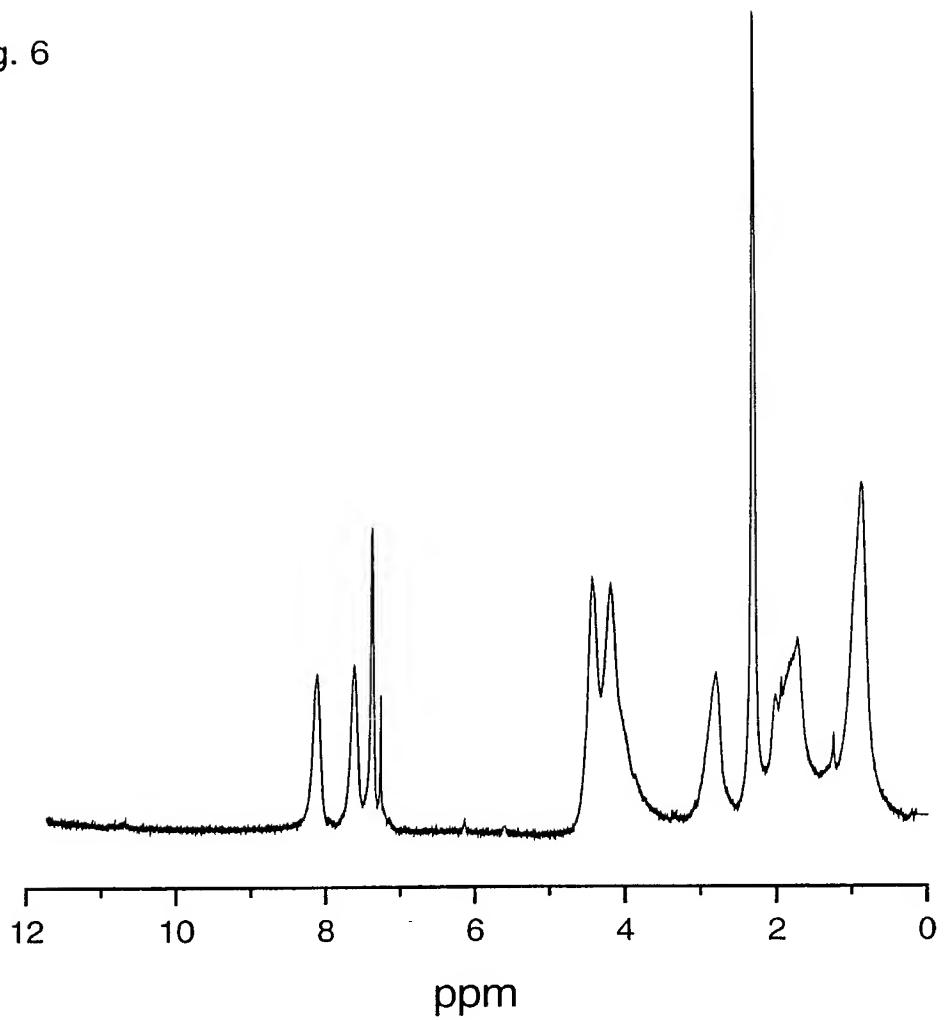
7/14

Fig. 5B

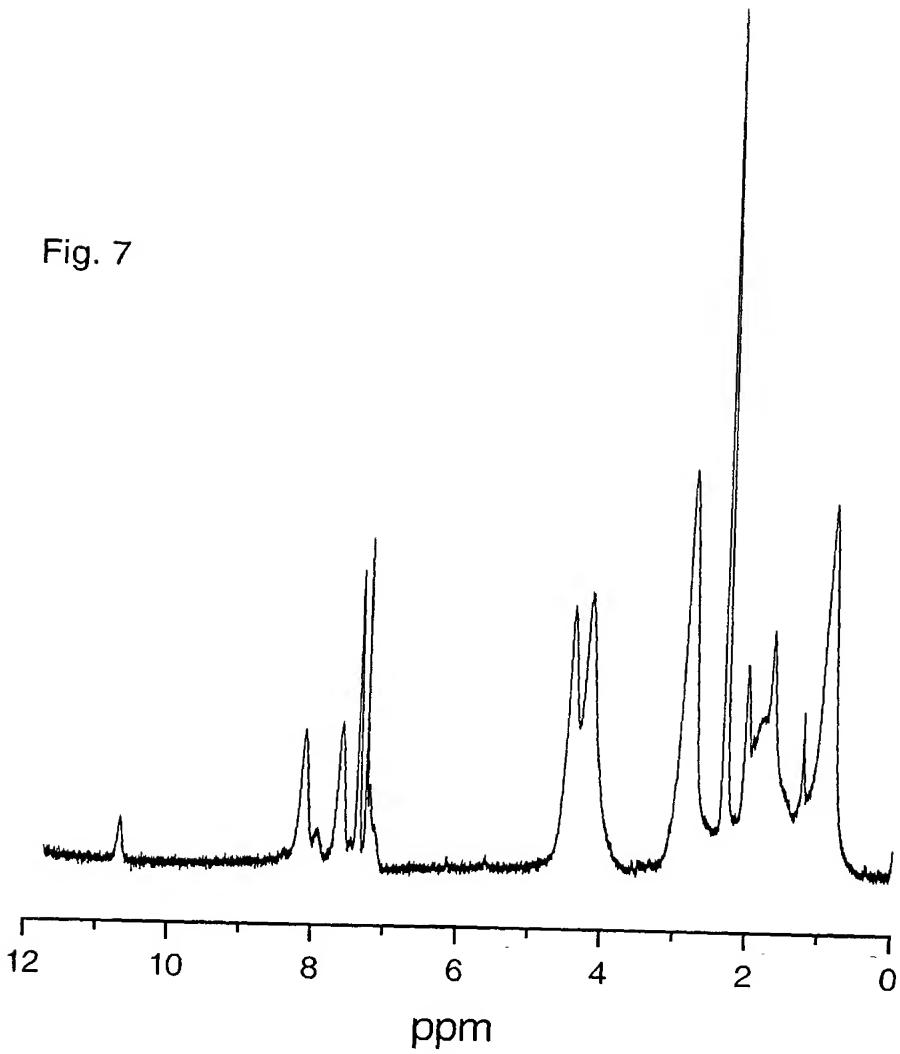


8/14

Fig. 6

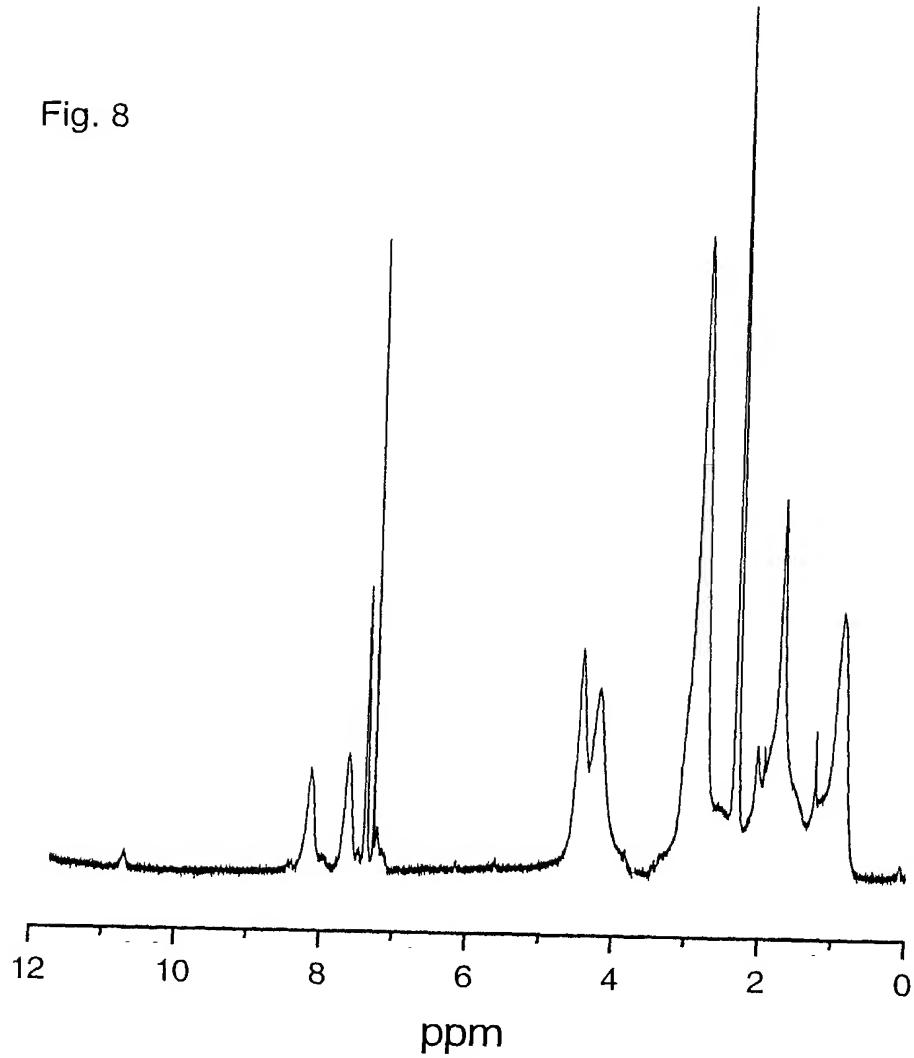


9/14



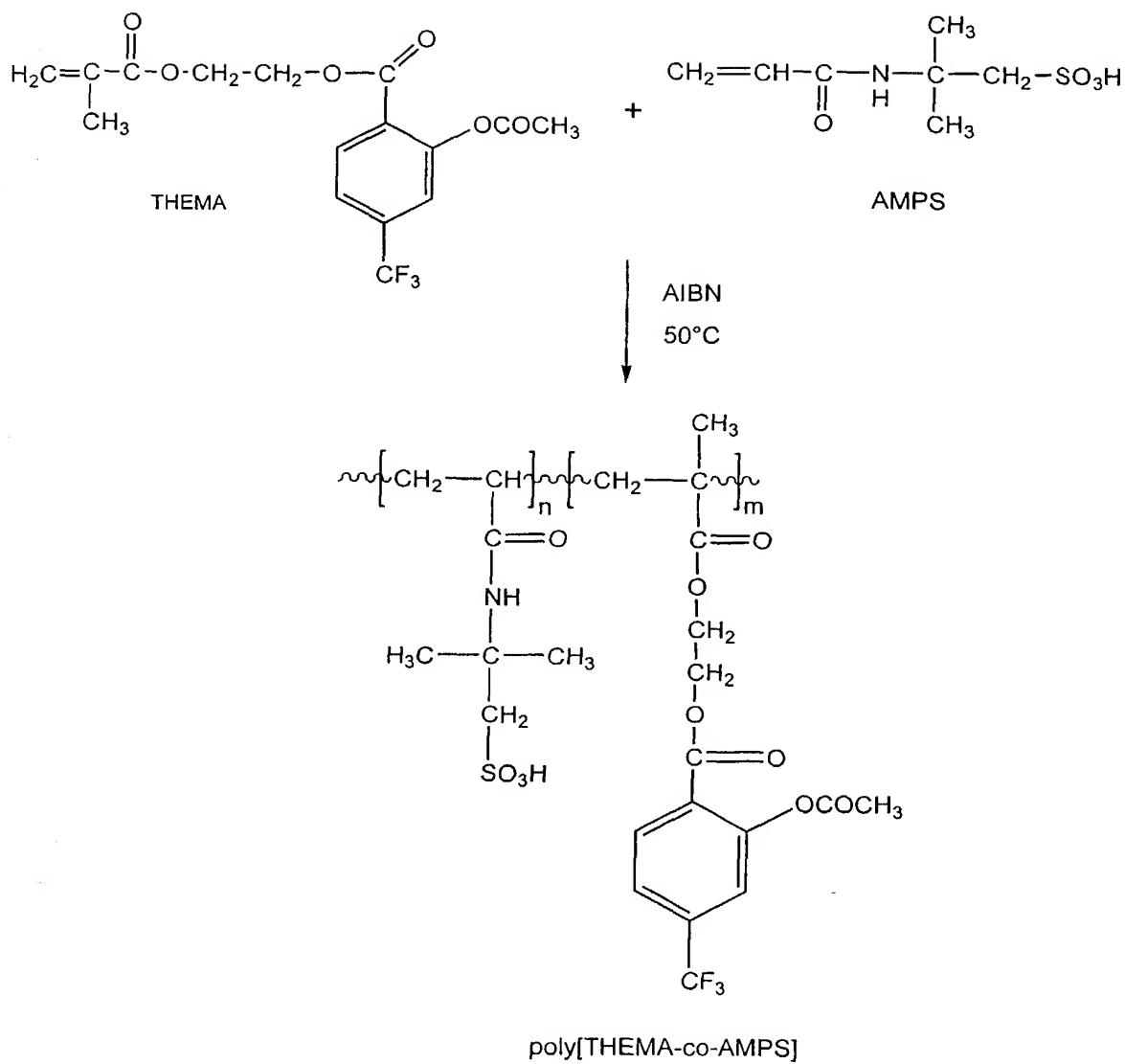
10/14

Fig. 8



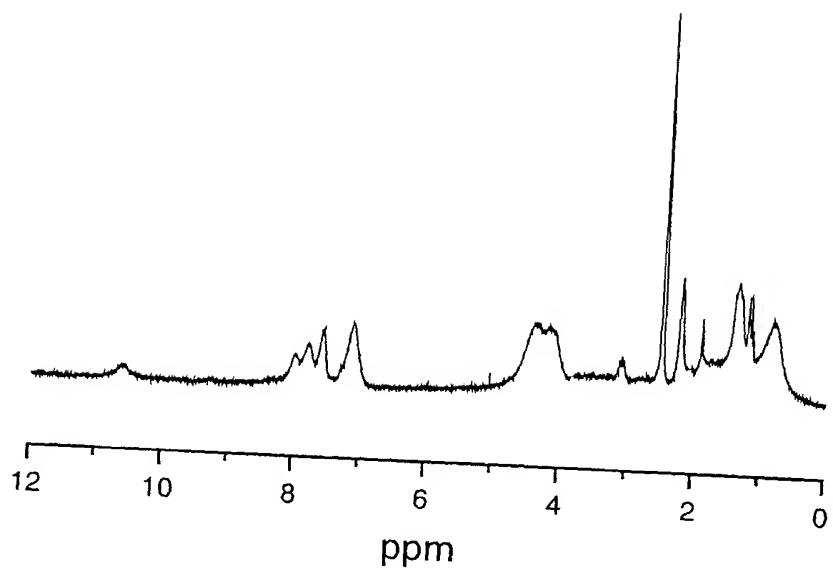
11/14

Fig. 9



12/14

Fig. 10A



13/14

Fig. 10B

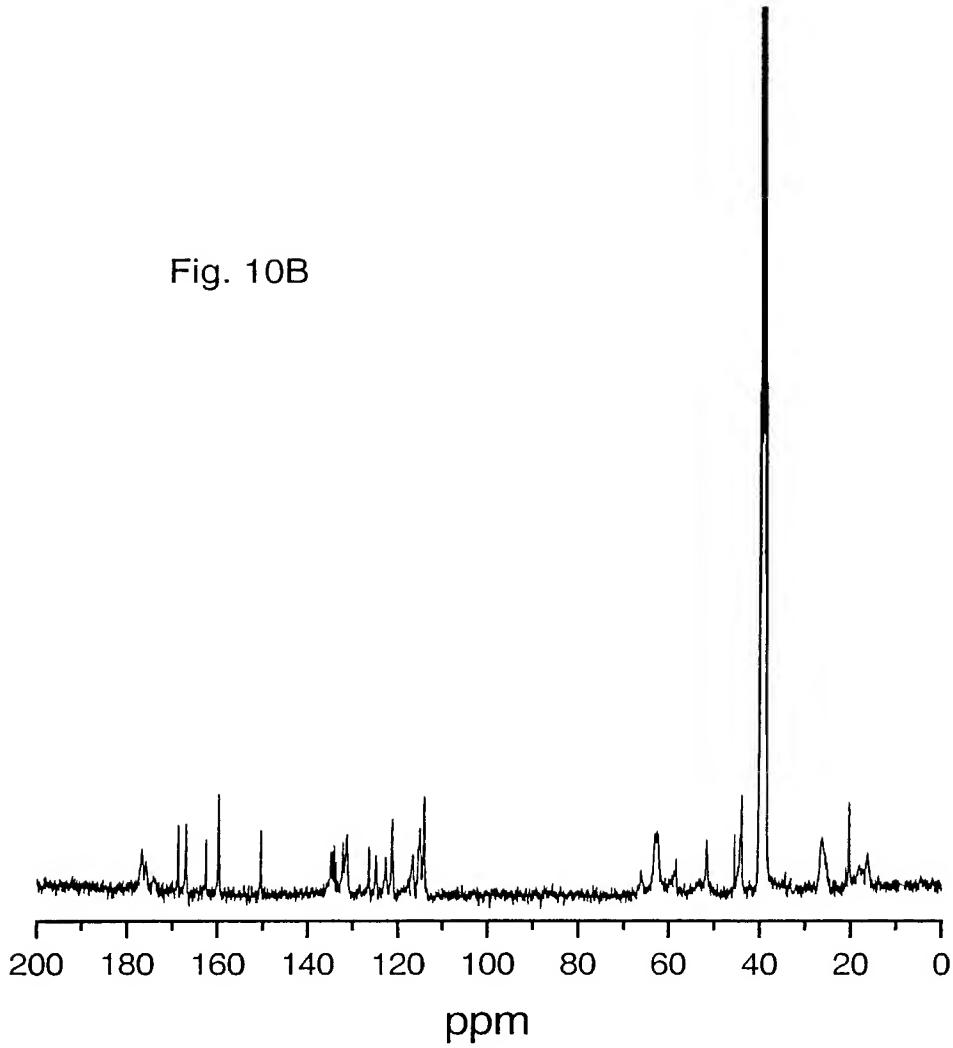
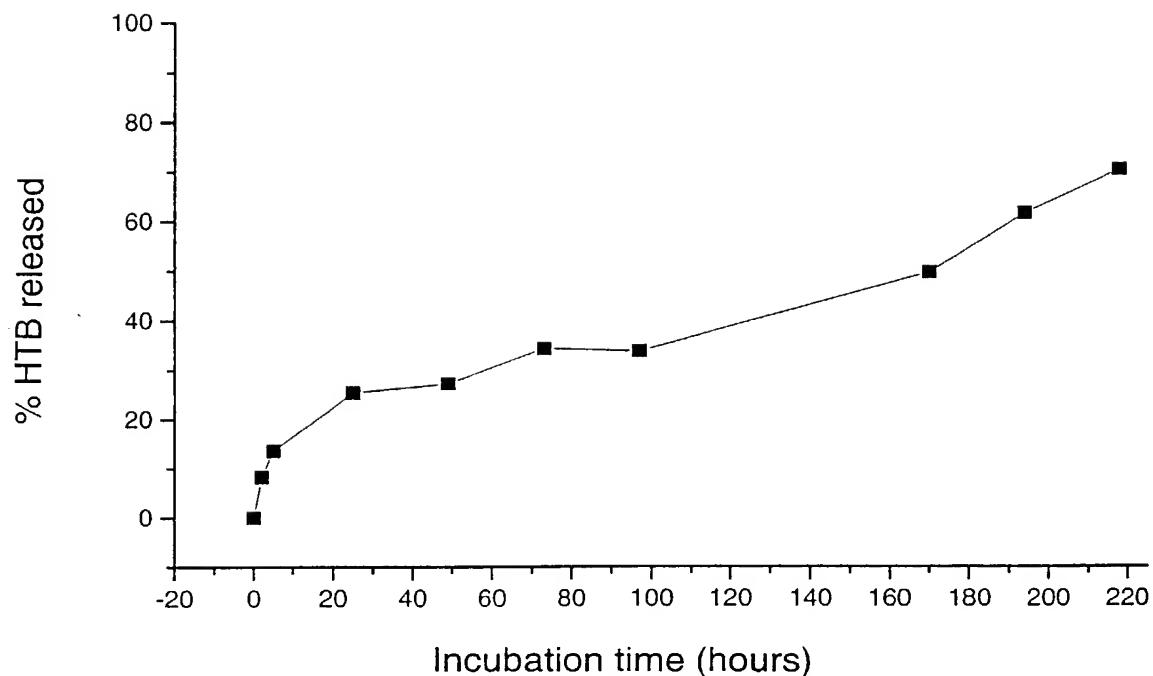


Fig. 11



**DECLARATION AND POWER OF
ATTORNEY FOR UTILITY OR DESIGN
PATENT APPLICATION
(37 CFR 1.63)**

Declaration
Submitted
with Initial
Filing

Declaration
Submitted
after Initial
Filing

Attorney Docket No.	1604-130
First Named Inventor	Alberto Gallardo Ruiz
COMPLETE IF KNOWN	
Application Number	Unassigned
Filing Date	March 4, 2002
Group Art Unit	Unassigned
Examiner Name	Unassigned

As a below named inventor, I hereby declare that.

My residence, mailing address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: NEW BIOCOPATIBLE POLYMERIC SYSTEMS CARRYING TRIFLUSAL OR HTB the specification of which was filed on September 1, 2000 as PCT International Application Number PCT/ES00/00335.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Numbers	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES NO
P9902013	ES	09/03/1999		

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

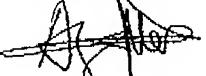
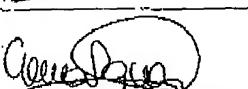
Application Number(s)	Filing Date (MM/DD/YYYY)

I or we hereby appoint the registered practitioner(s) associated with Customer No. 6449 to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Direct all correspondence to Customer Number 6449.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

J. THERIN

1936.7.1

NAME OF SOLE OR FIRST INVENTOR:		<input type="checkbox"/> A petition has been filed for this unsigned inventor	
Given Name (first and middle [if any]) Alberto		Family Name or Surname	Gallardo Ruiz
Inventor's Signature 		Date 30/04/2002	
Residence: City Madrid		Country SPAIN <input checked="" type="checkbox"/>	Citizenship SPAIN
Mailing Address Paseo de la Castellana, 127			
Mailing Address			
City Madrid		Postal Code 28046	Country SPAIN
NAME OF SECOND INVENTOR:		<input type="checkbox"/> A petition has been filed for this unsigned inventor	
Given Name (first and middle [if any]) Gema		Family Name or Surname	Rodriguez Crespo
Inventor's Signature 		Date 30/04/02	
Residence: City Madrid		Country SPAIN <input checked="" type="checkbox"/>	Citizenship SPAIN
Mailing Address Virgen del Sagrario, 25			
Mailing Address			
City Madrid		Postal Code 28027	Country SPAIN
NAME OF THIRD INVENTOR:		<input type="checkbox"/> A petition has been filed for this unsigned inventor	
Given Name (first and middle [if any]) Julio		Family Name or Surname	San Román del Barrio
Inventor's Signature 		Date 30/04/02	
Residence: City Las Matas		Country SPAIN <input checked="" type="checkbox"/>	Citizenship SPAIN
Mailing Address San Lorenzo del Escorial, 38			
Mailing Address			
City Las Matas		Postal Code 28290	Country SPAIN